A Model for the Free Radical and Electrophilic Hydroxylation of Bicyclo[2.1.0]pentane

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Abstract: Ab initio molecular orbital calculations have been used to model the stereochemistry of bicyclo[2.1.0]pentane hydroxylation. Equilibrium geometries and transition states were fully optimized at the MP2 level of theory using the 6-31G* and 6-31G** basis sets; all transition states were confirmed to be first-order saddle points by MP2 frequency calculations; energy differences and barrier heights were computed at the MP4 level with and without spin projection. Both the endo- and exo-bicyclo[2.1.0]pent-2-yl radicals are significantly pyramidal, but are nearly equal in energy (∆E < 0.3 kcal/mol) and are separated by a very low (<0.4 kcal/mol) barrier. The barrier for trapping the bicyclopropenyl radical by H2S is 1.5 kcal/mol lower for the endo radical. Even though the endo and exo bond strengths are nearly identical in bicyclo[2.1.0]pentane, abstraction of the endo hydrogen via the OH radical is favored over the exo hydrogen by 1.4 kcal/mol. Concerted oxygen insertion was modeled by reaction of bicyclo[2.1.0]pentane with water oxide, H2OO; the insertion transition state yielding the endo alcohol is 1.3 kcal/mol lower in energy. The endo preference of all the reactions in the present study can be attributed to cyclopropylcarbinyl stabilization of the transition states. The relevance of these calculations to cytochrome P-450 hydroxylation is discussed.

Introduction

One of the most intriguing oxidations mediated by cytochrome P-450 (P-450) involves the hydroxylation of unactivated carbon-hydrogen bonds.1 Early mechanistic studies suggested that oxygen atom transfer to the alkane substrate occurred by a concerted oxene insertion process. In many cases hydroxylation occurred with essentially complete stereoselectivity.2 With the increased capability to measure very fast reaction rate constants with essentially complete stereoselectivity.2 With the increased capability to measure very fast reaction rate constants, it was suggested that the multiplicity of substrate attachment in the active site probably imposes steric constraints on the transition state geometry. Newcomb et al.7a have measured the relative rate constants (kH/kθ) for ring opening of bicyclo[2.1.0]pent-2-yl radical (2) with RSH and have reported a value of kθ at 25 °C of 1.5 × 10−6 s−1. Highly stereoselective trapping of 2 with ArSD afforded exo-endo-bicyclo[2.1.0]pentane-3-2 in a ratio of 6:94. The small kinetic isotope effect (kH/kθ = 1.85) observed is consistent with a slight S-D bond breaking in the transition state for the exoetherium atom transfer reaction. It was suggested that the high stereoselectivity was a consequence of an electronic effect between the C-1-C-4 bond and the endo-C-2-H bond. Wiberg et al.8 have predicted on the basis of ab initio calculations at the HF/6-31G* level that the endo-C-2-H bond is 0.002 Å longer than the exo-C-2-H bond. Since endo trapping was favored by a ΔΔG° of about 1.1 kcal/mol, microscopic reversibility arguments have been used as a calibrated free-radical “clock”9 with which the rate of oxygen rebound (kθ) may be determined by measuring the ratio of insertion product 4 that is derived from bicyclo[2.1.0]pent-2-yl radical (2) to the amount of rearranged alcohol 5 resulting from capture of hydroxyl radical by cyclopent-3-enyl radical (3) (Scheme 1).

(1) has been used as a calibrated free-radical “clock”4 with which the ratio of insertion product 4 that is derived from bicyclo[2.1.0]pent-2-yl radical (2) to the amount of rearranged alcohol 5 resulting from capture of hydroxyl radical by cyclopent-3-enyl radical (3) (Scheme 1). Ortiz de Montellano and Stearns3 examined the P-450 hydroxylation of 1 and established a 7:1 ratio of unarranged (4) to rearranged (5) alcohols, suggesting that the oxygen rebound (kθ) is about seven times faster than the ring opening (kθ) of the bicyclo[2.1.0]pent-2-yl radical.10 Selective abstraction of the endo-C-2-H bond and formation of only the endo-C-2 alcohol 4 were ascribed to geometric constraints imposed by the enzyme active site. Newcomb et al.7a have measured the relative rate constants (kH/kθ) for ring opening of bicyclo[2.1.0]pent-2-yl and trapping of radical 2 with RSH and have reported a value of kθ at 25 °C of 1.5 × 10−6 s−1. Highly stereoselective trapping of 2 with ArSD afforded exo-endo-bicyclo[2.1.0]pentane-3-2 in a ratio of 6:94. The small kinetic isotope effect (kH/kθ = 1.85) observed is consistent with a slight S-D bond breaking in the transition state for the exoetherium atom transfer reaction. It was suggested that the high stereoselectivity was a consequence of a stereoelectronic effect between the C-1-C-4 bond and the endo-C-2-H bond. Wiberg et al.8 have predicted on the basis of ab initio calculations at the HF/6-31G* level that the endo-C-2-H bond is 0.002 Å longer than the exo-C-2-H bond. Since endo trapping was favored by a ΔΔG° of about 1.1 kcal/mol, microscopic reversibility arguments have been used as a calibrated free-radical “clock”4 with which the ratio of insertion product 4 that is derived from bicyclo[2.1.0]pent-2-yl radical (2) to the amount of rearranged alcohol 5 resulting from capture of hydroxyl radical by cyclopent-3-enyl radical (3) (Scheme 1). Ortiz de Montellano and Stearns3 examined the P-450 hydroxylation of 1 and established a 7:1 ratio of unarranged (4) to rearranged (5) alcohols, suggesting that the oxygen rebound (kθ) is about seven times faster than the ring opening (kθ) of the bicyclo[2.1.0]pent-2-yl radical.10 Selective abstraction of the endo-C-2-H bond and formation of only the endo-C-2 alcohol 4 were ascribed to geometric constraints imposed by the enzyme active site. Newcomb et al.7a have measured the relative rate constants (kH/kθ) for ring opening of bicyclo[2.1.0]pent-2-yl and trapping of radical 2 with RSH and have reported a value of kθ at 25 °C of 1.5 × 10−6 s−1. Highly stereoselective trapping of 2 with ArSD afforded exo-endo-bicyclo[2.1.0]pentane-3-2 in a ratio of 6:94. The small kinetic isotope effect (kH/kθ = 1.85) observed is consistent with a slight S-D bond breaking in the transition state for the exoetherium atom transfer reaction. It was suggested that the high stereoselectivity was a consequence of a stereoelectronic effect between the C-1-C-4 bond and the endo-C-2-H bond. Wiberg et al.8 have predicted on the basis of ab initio calculations at the HF/6-31G* level that the endo-C-2-H bond is 0.002 Å longer than the exo-C-2-H bond. Since endo trapping was favored by a ΔΔG° of about 1.1 kcal/mol, microscopic reversibility arguments 

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suggest that the endo-C-2 hydrogen in 1 must also be abstracted by PhS more readily than the exo-C-2 hydrogen, possibly reflecting the difference in bond strengths of the exo and endo hydrogens. The origins of this selectivity, however, are quite complex since the radical–radical coupling of radical 2 with the nitroxyl radical Tempa gave the exo adduct as the major product with an exo/endo ratio of 2.4:1.6.

In this report we will examine the electronic structure of bicyclo[2.1.0]pentane (1), its free radical, 2, and the relative reactivity of the exo and endo hydrogens of 1 toward abstraction, free-radical trapping, and electrostatic oxygen insertion.

Method of Calculation

Molecular orbital calculations were carried out using the Gaussian 92 program system utilizing gradient geometry optimization. Unrestricted Hartree–Fock and Möller–Plesset perturbation theories were used for all open-shell species; restricted methods were used for closed-shell systems. Preliminary geometries of the reactants and transition structures were first determined at the second- and third-order Möller–Plesset (MP2) level of theory with the 3-21G basis set. All geometries were then fully optimized with the 6-31G* or 6-31G** basis set using second-order perturbation theory unless noted otherwise. Relevant energies and barrier heights for oxygen insertion into 1 by water oxide were computed using fourth-order Möller–Plesset perturbation theory and the MP2-optimized geometry (frozen core, MP4SDTQ/6-31G*/MP2/6-31G* or MP4/6-31G**/MP2/6-31G**). Vibrational frequency calculations at the MP2 level were used to characterize these stationary points as either minima (zero imaginary frequencies), first-order transition states (a single imaginary frequency), or second-order saddle points, SOSP (two imaginary frequencies).

The potential energy surfaces for radical trapping of 2 with H2S were examined at the MP2/6-31G** (frozen core) level. Vibrational frequency calculations at the MP2/6-31G** level established both endo and exo transition states as first-order saddle points. The transition structures for endo and exo hydrogen abstraction from 1 with HO* were also calculated at the MP2/6-31G** (full) level, and an analytical frequency calculation at the same level of theory established both transition states to be first-order saddle points. Entropies were calculated in the rigid rotor–harmonic oscillator approximation (no special treatment for low-imaginary frequency), or second-order saddle points, SOSP (two imaginary frequencies).

Results and Discussion

Bicyclo[2.1.0]pent-2-yl Radical. Since the bicyclo[2.1.0]pent-2-yl radical (2) is the putative intermediate in P-450 hydrogenation of this hydrocarbon, we initiated this study with an examination of its geometry. MINDO/3 calculations have suggested that free radical 2 has a nonplanar radical center that is only 0.05 kcal/mol lower in energy than the radical when it was forced to be planar. The present ab initio calculations with full geometry optimization at the MP2/6-31G** hypersurface, with exo radical 2 predicted to be 0.19 kcal/mol more stable than endo radical 2 (Table 1). The deviation of the radical center from planarity, as measured by the C1–C2–C3–H1 dihedral angle (Figure 1), is −23.4° for the exo radical 2, while β is 36.6° for the endo radical. This is perhaps not too surprising because nonplanar cyclopropylcarbinyl cations have been invoked in the explanation of highly stereoselective solvolysis reactions.

Stereoelectronic effects due to cyclopropylcarbinyl stabilization also dramatically influence the rate of solvolysis of exo- and endo-bicyclo[2.1.0]pentyl 3,5-dinitro-2-benzoate, where a difference in activation enthalpy of 12 kcal/mol and an endo/exo rate ratio of 105 have been reported. The observed ratio of alcohols (4:5) derived from P-450 oxidation can also be influenced by rearrangement of 4 under the polar conditions of the experiment.

The transition state (TS-6) connecting the two nonplanar radicals has a very small activation barrier (0.39 kcal/mol) at the MP2/6-31G* level, and this activation barrier was found to be identical with the 6-31G* basis set. Although TS-6 was established to be a first-order saddle point by an analytical frequency calculation at the MP2/6-31G* level, the small barrier disappears when corrections for zero-point energy (ZPE) are added. Fourth-order Möller–Plesset treatment of electron correlation has essentially no effect upon the magnitude of these relatively small energy differences (Figure 1).

Radical Trapping with Dihydrogen Sulfide. Radical recombination reactions of bicyclo[2.1.0]pent-2-yl radical (2) with nitroxyl radical6 occurred predominantly from the exo face of 2, suggesting that C–O bond formation was controlled by steric factors. However, carbon–hydrogen bond formation in trapping experiments of radical 2 with ArSH proceeded almost exclusively (96:4) from the more hindered endo face. The stereoselectivity was reduced with the more reactive trapping agent ArSeH. An earlier transition state was implicated in the explanation of the reactivity differences.

In an effort to examine the stereo-electronic influence of the cyclopropylcarbinyl radical on the endo/exo ratio of radical trapping, we have examined potential energy surfaces for the reaction of radical 2 with H2S at the MP2/6-31G** level of theory. At the MP4/6-31G**/MP2/6-31G** level of theory the endo transition state (TS-7) has a predicted DE = 1.0 kcal/mol (Figure 2). The barrier height for hydrogen transfer from H2S to the endo face of 2 was 1.5 kcal/mol lower than radical trapping from the exo direction, in excellent agreement with experiment. With ZPE corrections the MP2/6-31G**/MP2/6-31G** barriers for TS-7 and TS-8 change by 0.03 and 0.17 kcal/mol. The MP4/6-31G**/MP2/6-31G** barriers heights for TS-7 and TS-8 are 0.44 and 1.79 kcal/mol, respectively. Note that the relative barrier heights for exo versus endo change by less than 0.3 kcal/mol on going from the MP2 to the MP4 level of theory. Both transition structures were established to be first-order saddle points at both
the MP2/3-21G and MP2/6-31G** levels. The increased steric interaction for endo trapping is reflected in the higher entropy of activation (ΔSΔ = 1.1 cal/mol K) for endo TS-7. The reported experimental ΔG° was 1.1 kcal/mol.7a It is of interest to note that the endo-C-2 hydrogen bond is 0.027 Å longer than the exo-C-2 hydrogen bond in the transition state (Figure 2). The 10% S–H bond elongation in TS-7 is also consistent with the relatively small isotopic effect (kS/kH = 1.85) for reported endo trapping of 2. The C1–C2 bond shortens and the C1–C3 bond elongates in the TS relative to hydrocarbon 1 (Figure 3) as a consequence of cyclopropylcarbinyl delocalization. Similar geometric changes are seen in the other transition states.

**Hydrogen Abstraction by Hydroxyl Radical.** Another of the fundamental questions that we wish to address in this study is the origin of the reactivity differences between the endo- and exo-C-2 hydrogens in bicyclo[2.1.0]pentane. At the MP2/6-31G** level the endo-C-2 hydrogen is 0.007 Å longer than the exo-C-2 hydrogen, reflecting a potentially weaker endo-C–H bond (Figure 3). However, exo and endo radicals are of nearly identical energy, and the bond dissociation energies of the exo- and endo-C-2 hydrogen bonds must also be nearly identical. The greater reactivity of the endo-C-2 hydrogen must therefore be a consequence of a transition-state phenomenon.

The hydroxyl radical is one of the simplest open-shell oxygen species that we could use to model hydrogen abstraction from 1. Hydrogen abstractions of this type require as a minimum the MP2 level of theory with a basis set that includes polarization functions on the hydrogen as well as the heavy atoms. The barrier height for abstraction of the endo-C-2 hydrogen from 1 by hydroxyl radical is predicted to be 6.81 kcal/mol at the MP4/6-31G** level of theory. Significantly, the endo-C–H bond in TS-10 has only been elongated 0.08 Å relative to ground state 1. However, the

<table>
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<th>compound</th>
<th>MP2/6-31G*</th>
<th>MP4/6-31G**//MP2/6-31G*</th>
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<th>MP4/6-31G**//MP2/6-31G**</th>
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<td>0.104 85</td>
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<tr>
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<td>-193.986 30</td>
<td>-193.972 91</td>
<td>-193.988 17</td>
<td>0.105 25</td>
<td></td>
</tr>
<tr>
<td>4 (endo)</td>
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<td>-269.630 16</td>
<td>-270.107 45</td>
<td>-270.249 30</td>
<td>0.143 54</td>
<td></td>
</tr>
<tr>
<td>5 (exo)</td>
<td>-269.630 16</td>
<td>-269.630 16</td>
<td>-270.107 45</td>
<td>-270.249 30</td>
<td>0.143 26</td>
<td></td>
</tr>
<tr>
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<td>0.121 09</td>
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<td>-270.247 14</td>
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<td>-270.107 33</td>
<td>-270.107 45</td>
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<td>0.143 26</td>
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The CI-C2 bond shortens and the C4–C5 bond elongates in the TS relative to hydrocarbon 1 (Figure 2) as a consequence of a transition-state phenomenon. Another of the fundamental questions that we wish to address in this study is the origin of the reactivity differences between the endo- and exo-C-2 hydrogens in bicyclo[2.1.0]pentane. At the MP2/6-31G** level the endo-C-2 hydrogen is 0.007 Å longer than the exo-C-2 hydrogen, reflecting a potentially weaker endo-C–H bond (Figure 3). However, exo and endo radicals are of nearly identical energy, and the bond dissociation energies of the exo- and endo-C-2 hydrogen bonds must also be nearly identical. The greater reactivity of the endo-C-2 hydrogen must therefore be a consequence of a transition-state phenomenon.

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C$_2$-H$_3$ and C$_2$-H$_2$ bond lengths in TS-9 and TS-10 are essentially identical. The relatively low magnitude of this barrier height is also consistent with this exothermic ($\Delta E = -10.7$ kcal/mol) hydrogen atom transfer reaction. The importance of removing unwanted spin states from the UHF wave function for hydrogen abstraction by HO has been established.$^{13}$ As expected, the PMP4/6-31G* barriers for TS-9 and TS-10 are lowered by 1.08 and 1.14 kcal/mol, respectively; nevertheless, the relative barriers ($endo$ vs $exo$) consistently agree to within ±0.3 kcal/mol at the MP2, MP4, and PMP4 levels of theory. By comparison the barrier heights for the reaction CH$_3$ + OH $\rightarrow$ CH$_2$ + HOH with and without spin projection are 9.05 and 10.37 kcal/mol, respectively (MP4SDTQ/6-311G**).$^{13}$

Since the difference in energy between $endo$ and $exo$ radical

Hydroxylation of Bicyclo[2.1.0]pentane

Scheme 2. Hydrocarbon Fragment Orbitals for a Disubstituted Methylene Group that Can Interact with an Electrophile E

2 is extremely small, these data suggest that the faster rate of abstraction of the endo-C-2 hydrogen is attributable to a stabilizing stereoelectronic effect of the cyclopropylcarbinyl system in the transition state for abstracting the endo relative to the exo-C-2 hydrogen in 1. Our calculations are consistent with the earlier work of Newcomb et al.1 for the preferential trapping with ArSH on the endo face of radical 2. Both experimental7 and theoretical data implicate the adjacent cyclopropyl ring in 1 as the origin of the rate differences for both making and breaking the endo-C-2 hydrogen bond of 1. Since the trapping of free radical 2 with Tempo does not involve C-H bond making, one should not anticipate a stereoelectronic influence, and the radical–radical recombination should be subject only to steric considerations. Both TS-7 and TS-9 may be considered as hydrogen abstraction (C–H) reactions from bicyclo[2.1.0]pentane by HS' and HO'. Though one is a late TS and the other an early TS, both of the transition states are influenced stereoelectronically by the adjacent cyclopropyl ring.

Electrophilic Hydroxylation by Water Oxide. The above theoretical analysis and prior experimental data suggest that the stereoselectivity of endo hydroxylation is consistent with a stereoelectronic stabilization of the transition state affording secondary cyclopropylcarbinyl radical 2. Although the weight of evidence for cytochrome P-450 hydroxylation supports the oxygen rebound mechanism, the possibility that a concerted oxene-insertion pathway intervenes with some enzymatic systems cannot be excluded. Ring opening of diphenyl-substituted cyclopropylcarbinyl radicals to give a rearranged radical has been measured to proceed at room temperature with exceptionally high rates (k = 5 × 10^{11} s^{-1}). In order for hydroxylation to proceed without rearrangement, KOH must be greater than k, (Scheme 1). These data lend credence to the suggestion that carbon–oxygen bond formation may not proceed through formation of a cyclopropylcarbinyl radical or cation. Hydroxylation of bicyclo[2.1.0]pentane with cytochrome P-450 afforded only endo alcohol 4 (Scheme 1), while MMO gave approximately an equal amount of exo and endo insertion products.14 Cogent arguments were presented that MMO hydroxylation with selected substrates can involve direct oxygen insertion without the intermediary of a free radical. This interesting mechanistic dichotomy promoted us to examine the endo/exo stereoselectivity for electrophilic hydroxylation of bicyclo[2.1.0]pentane.

We have recently described a frontier molecular orbital (FMO) model for the activation of saturated hydrocarbons that provides a rationale for the orientation of approach of the electrophile and an explanation for the observed stereoselectivity for insertions into carbon–hydrogen bonds. In this FMO model we dissect the hydrocarbon into doubly occupied fragment orbitals that have σ- and π-symmetry. For example, pertinent canonical Hartree–Fock molecular orbitals for the secondary carbon of propane are given in Scheme 2. In this model the electrophile E has an empty electrophilic orbital and one or more pairs of electrons that serve as the terminus for a concerted 1,2-hydrogen migration in the transition state for electrophilic insertion of E into a C–H bond. In the transition state the electrophile E approaches the fragment orbital along the axis of the filled atomic carbon p orbital, and a 1,2-hydrogen migration to an adjacent lone pair of electrons takes place in concert with C–E bond formation. The localized description of the C–H bond is equally valid, but it is more difficult to visualize the trajectory of the electron-donating and accepting orbitals.

Water oxide has recently been predicted to exist as an energy minimum on the potential energy surface for the 1,2-hydrogen
migration in hydrogen peroxide (HOOH → H₂O₂).¹⁵c,¹⁵ We have utilized water oxide (H₂O−O) as a model oxygen atom donor in the oxidation of amines to amine oxides¹⁵c and the oxidation of saturated hydrocarbons to alcohols.¹⁵b We have established that the MP2/6-31G* level of theory is adequate for predicting geometries and fourth-order Møller–Plesset perturbation theory (MP4) for describing potential energy surfaces involving heterolytic cleavage of the O−O bond in water oxide.¹⁵d

In earlier studies on a series of saturated hydrocarbons we found that electrophilic oxygen approaches the hydrocarbon along the atomic orbital comprising a πCH₂ fragment orbital (Scheme 2),¹⁵b while carbene insertion typically involves interaction with a doubly occupied σCH₂ fragment orbital.¹⁵b Interaction of both electrophiles with πCH₃ and σCH₃ orbitals gave higher activation barriers due to increased steric interactions. The primary pathway for oxygen atom insertion in the πCH₂ orientation can be envisaged as the interaction of the empty σ* orbital of the O−O bond of water oxide with the doubly occupied πCH₂ fragment orbital. In the transition state the CH₂ bond is broken as hydrogen H₁ migrates the adjacent oxygen, affording the alcohol insertion product (eq 3). In a similar fashion the σCH₃ orbital can mix with the σ*O−O orbital and displace water as a neutral leaving group in concert with hydrogen migration (eq 4) (see Scheme 3).

Because of the structural complexity of the bicyclic hydrocarbon 1 and the number of basis functions involved (135), we first examined "idealized transition states" for endo and exo oxygen insertion by water oxide (Figure 4). In these orientations the O₁-C₇−H₁−H₂ dihedral angle is constrained to be planar. Molecular models suggest that the least sterically hindered pathways for oxygen atom transfer to 1 would appear to be σCH₂ endo and exo orientations 11 and 12 (Figure 4). The endo insertion pathway 11 is 0.83 kcal/mol lower in energy than corresponding exo insertion 12, involving migration of hydrogen H₁ at the MP4/MP2/6-31G* level (Table 1). However,

**Figure 4.** Idealized endo σCH₂ (11), exo σCH₂ (12), endo πCH₂ (13), and exo πCH₂ (14) orientations for oxygen atom transfer from water oxide to bicyclo[2.1.0]pentane. Structures 11 and 12 are SOSP, while 13 and 14 have nonzero gradients. The dihedral angle of the shaded atoms in each figure is constrained to be planar. Geometries are at the MP2/6-31G* level, distances are given in angstroms, and angles are in degrees. Barrier heights are given in kilocalories/mole.
analytical frequency calculations established both structures to be second-order saddle points (SOSP). The second imaginary frequency corresponds to a rotation from the $\sigma_{CH}$ to the endo $\sigma_{CHR}$ orientation (see TS-15).

The geometrically constrained $\pi_{CH}$ orientations for endo (13) and exo (14) hydroxylation were also examined, and all variables were optimized with the exception of the O-I-C-H$_2$-$H_3$ dihedral angle denoted by the shaded atoms (Figure 4). The two pathways differed by only 0.50 kcal/mol, with a slight preference being observed for the endo direction (Table 1). However, both "transition structures" had nonzero forces in the constrained dihedral angle. Release of this geometry constraint resulted in fully optimized transition structures (Figure 5) that were confirmed to be first-order saddle points by analytical frequency calculations at the MP2/6-31G* level. The barrier for the endo approach in TS-15 was 1.3 kcal/mol lower in energy than exo TS-16. The ZPE corrections for TS-15 and TS-16 are $-1.97$ and $-2.15$ kcal/mol, respectively. This fully optimized exo transition structure is only 0.16 kcal/mol lower in energy than the idealized endo $\sigma_{CHR}$ approach (see Scheme 2 with the empty $\sigma^*$ orbital of water oxide. The O-I-C-H$_2$-$H_3$ dihedral angle in TS-15 is only $8.4^\circ$ out-of-plane. Electronic factors appear to favor the more hindered endo $\sigma_{CHR}$ approach. The barrier height for TS-15 (5.33 kcal/mol) is 1.0 kcal/mol lower in energy than the idealized endo $\sigma_{CHR}$ approach described in SOSP 11 (Figure 4). By comparison, the activation energy for the comparable oxidation of propane at C$_2$ is 3.9 kcal/mol for the $\pi_{CH}$ orientation. We suggest that the cyclopropylcarbinyl stabilization of the developing positive charge attending hydrocarbon migration is largely responsible for the endo selectivity observed. The alcohol insertion products 4 and 5 were fully optimized at the MP2/6-31G* level, and endo alcohol 4 is predicted to be more stable than its exo isomer by 1.3 kcal/mol.

We conclude from these data that the cyclopropylcarbinyl moiety in bicyclo[2.1.0]pentane (1) can exert its stereoelectronic influence on both the free-radical and electrophilic pathways for hydroxylation. This raises a question about the differences in the active site for P-450 versus MMO hydroxylation of 1. Since it appears that electronic effects slightly favor endo hydroxylation, the lack of endo/exo selectivity in MMO hydroxylation could be attributed to less steric requirements at the active site. However, this suggestion must be reconciled with a rebound rate ($k_{OH}$) that is greater than the rate of radical rearrangement ($k_1 = 1.5 \times 10^9$ kcal/mol).
If hydrogen abstraction occurs from the *endo* face of 1, then in order to form the *exo* alcohol in accordance with Scheme 1, either substrate 1 must rotate to expose its *exo* face or the hydroxyl radical must migrate to the *exo* face of radical 2. Reduced mass considerations militate against dynamic motion of either the iron center or the higher molecular weight hydrocarbon substrates on the reaction surface for the oxygen rebound step ($k_{OH}$). Dynamic rate theory considerations suggest that the lighter hydroxyl radical should migrate to the carbon radical center in the bound substrate in the rebound step. The frequency factor $k_T/h \sim 10^{13}$ seems to be the upper limit for rates of chemical change where nuclei, rather than just electrons or energy, change their position. The hydroxyferryl complex and the carbon–radical center must constitute an “intimate complex” in order for the Fe–OH bond to homolytically break and form a C–OH bond with rate constants approaching $10^{13}$. Consistent with this concept, an increase in molecular size of the hydrocarbon substrate could result in a greater van der Waals attraction for the charged ferryl center, a tighter binding, and a faster rebound rate as a consequence of its increasing polarizability. As the polarizability of the neutral becomes larger, a charge-induced dipole force can result in a deepening of the initial electrostatic potential well, and in principle this could overcome the intrinsic barrier to hydroxyl insertion. In the case of methane hydroxylation by MMO both carbon and oxygen radicals are of approximately equal mass and both could migrate accordingly in the rebound step. The above arguments are consistent with a concerted oxygen insertion process for those hydrocarbon substrates that exhibit very rapid radical rearrangement ($k_r$).

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